#6

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Bonnie DAVIS
Serial No.: 819,141 Group No.: 125
Filed: January 15, 1986 Examiner: Friedman
For: METHOD OF TREATING ALZHEIMER'S DISEASE

Commissioner of Patents and Trademarks
Washington, D.C. 20231

SIR:

L E T T E R

The purpose of this letter is to submit the documents referred to of the response of September 9 that were not submitted therewith, to clarify the remarks in that response to certain of these references and to submit copies of additional pieces of art which have come to light since that response was filed.

We now enclose copies of the following:

Acta Anesth Scand (1980) 21:166 referred to on page 2 of the response;

English translation of Summary of Russian language paper in Biull Exp Biol Med (1977) 83:185 referred to on page 5 of the response;

Psychopharmacology (1977) 52:251, referred to on page 5 of the response;

CERTIFICATE OF MAILING (37 CFR 1.8a)

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to the: Commissioner of Patents and Trademarks, Washington, D.C. 20231

JOHN RICHARDS
(Type or print name of person mailing paper)

Date: December 15, 1986

(Signature of person mailing paper)

J Am Geriat Soc 1977 25:1, referred to on page 5 and 8 of the response;

Pages 582-3 of The Pharmacological Basis of Therapeutics referred to on page 6 of the response;

Strategies for the Effective Treatment for Senile Dementia, p 177 referred to on pages 6 and 8 of the response;

Behavioral Biology (976) 16 p 387 referred to on page 6 of the response;

J Pharm Pharmac (1977) 29:110, referred to on pages 6 and 7 of the response;

Pharmacol Biochem Behav (1976) 5:(Suppl.1) 41, referred to on page 6 of the response;

Physiol Behav (1975) 14:563, referred to on page 6 of the response;

Pharmacol Biochem Behav (1974) 2:663, referred to on page 6 of the response;

Physiol Behav (1974) 13:381, referred to on page 7 of the response;

Hormones, Behavior and Psychopathology, pages 1, 3, 4 and 6-8 referred to on pages 7 and twice on page 8 of the response;

Neural Mechanisms in Learning and Memory, p 483 referred to twice on page 7 and twice on page 8 of the response;

Pharmacol Biochem Behav (1976) 4:703, referred to three times on page 7 of the response;

Pharmacol Biochem Behav (1974) 2:557, referred to twice on page 7 of the response;

Behav Biol (1977) 20:168, referred to on page 7 and twice on page 8 of the response;

English Summary of Arzneim-Forsch (1976) 26:1947, referred to on page 7 of the response;

Acta Physiol Pharmacol Bulg (1976)2:49, referred to twice on page 7 of the response;

Behav Biol (1975) 15:245), referred to on page 7 of the response;

Brain Res (1975) 84:329, referred to on page 7 of the response;

Arch Int Pharmacodyn (1974) 211:123), referred to on page 7 of the response;

Neural Mechanisms in Learning and Memory, p.508, referred to on pages 7 and 8 of the response;

Pharmacol Biochem Behav (1976) 4:123, referred to on page 7 of the response;

Curr Med Res Opin (1976) 4:303, referred to on page 8 of the response;

Psychopharmacology (1976) 49:307, referred to on page 8 of the response;

J Nerv Ment Dis (1976) 163:59, referred to on page 8 of the response;

J Comp Physiol Psychol (1976) 90:1082, referred to on page 8 of the response;

Psychopharmacology: A Generation of Progress, p. 1525 referred to on page 9 of the response;

J Am Geriat Soc (1977) 25:289, referred to on page 9 of the response; and

Neurobiology of Aging (1985) 6:95, referred to on page 9 of the response.

Copies of J Med Chem (1986) 29:1125 referred to on pages 6 and 8 and of J Clin Hosp Pharmac (1985) 10:327 referred to on pages 2, 8 and 9 of the response were submitted with the previous response.

A review of these references has revealed a few minor

discrepancies in the previous response as filed, although these do not affect the validity of any of the submissions made.

First at page 5, line 28 of the response, the specific reference to methamphetamine is misleading since the reference does not refer to this drug. The substance of statement made is, however, correct. The reference in fact refers to the use of methylphenidate. According to Goodman et al , the Pharmacological Basis of Therapeutics, methylphenidate is therapeutically interchangeable with the amphetamines.

At page 5, line 30, the reference to J Am Geriat Soc is wrong. The reference should have been to J Med Chem (1986) 29:1125.

There is a typographical error at page 6, line 22 of the response. As is clear from the papers referred to three year period in question was 1974-77.

A reconsideration of the papers listed as showing prior studies of compounds said to have effect on the facilitation of memory in humans or animals without brain lesions leads to a conclusion that the total number of compounds noted rather than being 39 should have been either 37 or 45 depending upon whether each of the ACTH fragments noted in the Hormones Behavior and Psychopathology reference is regarded as being one or several compounds.

At page 7, line 17, the reference cited in support of the studies on imipramine was wrong. It should have been Rosenzweig MR, Bennett EL eds Neural Mechanisms in Learning and Memory MIT Press Cambridge p. 483. A copy is enclosed.

At page 7, line 18, the reference support in support of studies on ß-lipotropin was wrong. The correct reference was J Pharm Pharmac 29:110. A copy is enclosed.

At page 8, line 6, the second reference to studies on strychnine is wrong. The correct reference is Acta Physiol Pharm Bulg (1976) 2:66. A copy is enclosed.

At page 8, line 19 "ACTH 4-10" should read "ACTH fragments" as the second reference used ACTH 4-9. However, any fragment of ACTH 1-10 containing 4-7 has equal potency. (Hormones, Behavior and Psychopathology, Sachar, 1976, p. 3).

At page 8, line 25, the second reference to studies using methylphenidate is wrong. The correct reference is J Med Chem 29:1125.

Furthermore, the reference to J Am Geriat Soc (1977) 25:289 should be ignored in the discussion of vasopressin at page 9, line 3 since the article does not refer to this compound, although the other two papers cited do so.

Finally, the applicant wishes to draw the Examiner's attention to some additional pieces of prior art that have only now been found or of which she was aware previously, but had not looked at for a prolonged period that contain information relating to the properties of galanthamine. These are as follows:

Baraka & Harik JAMA Vol. 238 pages 2293-4 (1977) - discusses use of galanthamine to reverse scopolamine-induced central anticholinergic syndrome;

Tonkopii and Prozorovskii in Byul Eks Bio i Med Vol. 82 pages 823-25, available in translation from Plenum Publishing Co., New York describe a study of the interaction of galanthamine in mouse brain acetylcholinesterase <u>in vivo</u>;

Wislicki in Brit J Anaesthesia 39:963 (1967) compares galanthamine with neostigmine as an antagonist non-depolarizing muscle relaxants;

Stojanov in European Trends in Anesthesiology International Anesthesiology Clinics describes the use of galanthamine as a curare antidote; and

Gujaral in Indian Pediatrics March 1965 page 89 describes the use of galanthamine in treating post-polio paralysis and pseudohypertrophic muscular dystrophy.

Gopel and Bestrain in Psychiat Neurol Med Psychol Leipzig 23 pages 712-718 review a number of uses that have been proposed for galanthamine including peripheral, facial paresis, peripheral cranial nerve paresis, peripheral neuropathy, mono and polyneuropathies radiculitis, cerebral vascular paralyses apoplexy and inflammations without substantial spasticity, progressive muscular dystrophy, collagen disease, multiple sclerosis, Friederick's disease and a myotrophic lateral sclerosis.

Copies of these papers are enclosed.

This additional art demonstrates that despite the fact that galanthamine has long been available and many of its properties are well known, there has been no suggestion of its use for treatment of Alzheimer's disease and support the Examiner's finding of patentability in this case.

Respectfully submitted,

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